

Primary prevention in cardiovascular disease: moving out of the shadows of the truth about death

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Abstract

Aim: This review identifies deficits in current educational efforts for the primary prevention of cardiovascular disease.

Data synthesis: Essential fatty acids in the foods we eat have a subtle but powerful influence on hundreds of different processes in the life and death of humans, understanding of which has been delayed by two attitudes in the biomedical community. One involves a bias towards expensive curative/treatment interventions that neglect prevention of initial nutritional causes of disease and death, and the other involves careless logic in interpreting evidence of causes of disease and death. Both attitudes interfere with translation of published science of essential fatty acids into effective prevention of cardiovascular deaths, a situation made worse by a widespread wish for simple descriptions of complex interactions in disease. Some clinical signs and risk factors may be only shadows of true causal factors. For example, attention to cholesterol ignored important evidence that nutritional imbalances in expenditure/intake of energy and in omega-3/omega-6 essential fatty acids cause cardiovascular disease. Balancing the few percentage of daily calories in omega-3/omega-6 nutrients is not a question of obesity or blood cholesterol. Effective prevention through education will require targeting the causal risk factors that are known beyond the shadow of a doubt, but seldom discussed by health professionals and the public.

Conclusions: Death from coronary heart disease comes from acute ischemia and arrhythmia, often following long-

term chronic inflammatory vascular damage that predisposes to acute fatal thrombosis and arrhythmia. The three processes involve excessive self-healing actions of natural n-6 autacoids (auto=self, akos=healing) produced from tissue essential fatty acids that come only from foods. Readily corrected nutritional imbalances in expenditure/intake of energy and in omega-3/omega-6 essential fatty acids are causal risk factors with plausible mechanisms contributing to fatal events which can be prevented.

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Health economics and primary prevention

Health economists calculate cost-effectiveness of therapeutic treatments in monetary terms, often providing marketing advantages for various competing curative/treatment protocols (1). Greater “effectiveness” comes from expensive/profitable pharmaceuticals and treatments only for individuals with recognized clinical signs and risk factors who are likely to progress soon to death. However, the busy marketing/professional dialog fails to evaluate population-based initiatives that benefit the broader population by preventing the underlying causes of the disease *before* clinical signs appear (2). Economic forces within the global health and illness industry create a bias towards treatment and secondary prevention and towards investments in increasingly high technology. This bias shifts health policy agendas towards short-term efforts that benefit the highest-risk individuals with higher education and higher incomes while neglecting prevention of initiating causes and leaving high morbidity and mortality rates among the people least likely to comprehend and reduce their own risks (3).

The result for cardiovascular disease (CVD) is a progressive year-to-year increase in the number of hospital dis-

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charges for treated CVD with no decrease in hospitalization for a first myocardial infarction (4). Without a conscious national choice of population-wide prevention that resists global food marketing forces, the growing worldwide convergence of eating patterns will likely lead to a steady state in which CVD is endemic and pandemic around the globe with CVD rates being varied more by education and income than by country. Such a globalized CVD epidemic would become the leading cause of death for humans, regardless of location on earth, making the ethics of CVD primary prevention a special concern worldwide.

Continuity of care of individual patients is managed by a system of professional clinical ethics (and insurance reimbursements), but there are few strategies (or funds) to devise and implement community-wide some continuity of health promotion and disease prevention. We have no formula to allocate resources between curative and preventive health actions or to estimate the potential gains in quality of life, years without disability, more productivity, and controlled health care costs. Primary prevention should begin before a person has any clear signs of pathology. When successful, prevention efforts decrease risky behaviors that expose people to infectious and toxic materials in the environment, and success with healthy air, water, and food is indicated by a high proportion of healthy elderly people in the population.

In contrast, secondary prevention begins only after an individual has signs or symptoms of abnormal pathology that predict an earlier death. In this case, the opportunity to prevent the initial exposure or onset of the disease for that individual has passed, and efforts are directed to treating the signs and slowing the progression of the disease. Here, too, success gives a high proportion of elderly people in the population, but the incidence of disorders is greater. Sadly, over half of the people who die suddenly of CHD have no prior symptoms considered worthy of medical treatment (5). Are scientists ethical to withhold community-wide primary prevention advice and only treat people with clinical signs of disease? The public health profession has failed to translate the published science regarding excessive essential fatty acid actions in chronic diseases into policy options and into effective communication to government, decision makers, and the public. This review focuses on the chain of events that links diets to the commonest worldwide cause of death of adults (6), cardiovascular disease (CVD) with coronary heart disease (CHD). The wide diversity in tissue eicosanoid precursors and CHD mortality rates among different nations (7-9) suggests that some populations have unknowingly developed primary prevention actions with food choices that others may wish to employ.

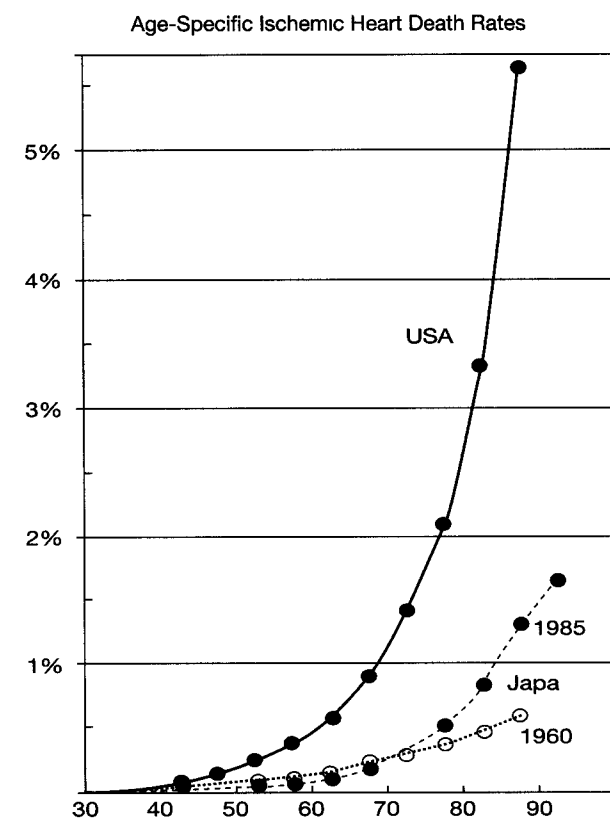
Let death wait

The good news is that at any given moment, most people do *not* die. The bad news is that sooner or later, everyone dies. The dynamics of when and how death will occur are a challenge faced by every human. Answers lie in understanding the long chain of events that move from conditions that are preventable and reversible to those that are inevitable and irreversible. A rising risk of death with increased age (Fig 1) reflects, in part, missed early opportunities to avoid the irreversible processes that progressively make death inevitable (8).

Age-specific death rates show a rising inevitability of death as people accumulate combinations of risk factors, none of which alone may be fatal. The dramatically accelerated rate of cardiovascular death with age prompts efforts to understand the causes of death and to prevent or delay

FIGURE 1

Accelerated risk of death with age. Age-specific rates (vertical axis) fit the age-cohorts noted on the horizontal axis. Modified from (8) with permission.



them. Recognizing that current voluntary food choices of Americans have imbalances in the expenditure/intake of energy and in the omega-3/omega-6 essential fatty acids that cause accelerated mortality (7, 9) will aid successful prevention. The past decade brought much public attention to healthy energy balance, but more attention to essential fatty acid balance is needed.

Concern about age-specific death rates is low among 20-40 year-old adults for whom visible clinical signs of disease are low, even as their increasing inflammatory vascular damage (10) sets the stage for the explosive rise of mortality rates later in life. As in an earlier report of young soldiers killed in Korea (11), autopsies showed fatty streaks in abdominal aortas of about 20% of 15- to 19-year-old subjects and nearly 40% of 30- to 34-year-old subjects (10). Raised fatty streaks were present in the right coronary arteries of nearly 10% of 15- to 19-year-old subjects and approximately 30% of 30- to 34-year-old subjects (12). The onset and progression of inflammatory vascular damage is usually well established before the age of forty or fifty when fatal signs of cardiovascular disease begin to appear as a statistically significant problem (Fig 1). With the rate of progression of further vascular damage predicted by the current number of plaques, the explosively accelerating curve of age-adjusted death rates with age brings death with greater certainty with advanced age. Unfortunately, attention directed to older patients with severe advanced cardiovascular problems tends to ignore the early diet-based causal mechanisms that started the chain of events in the disease (13) and the tissue imbalances that need correction by primary prevention efforts.

When 200 of 100,000 people die in one year, the 99,800 people who did not die have decisions to make about what preventive intervention seems reasonable to avoid such death in the coming year. What will they decide if the two hundred deaths resulted from thirty years of repeated missed personal opportunities to prevent the initial onset of pathology? Were the missed opportunities a result of fully informed voluntary choices of the people who died? Should anyone other than the affected person take responsible action for deaths caused by voluntary behaviors? Were the people fully informed and reconciled to an early death? If not, prevention efforts are appropriate. Clinicians who focus on treating individual patients need clearer advice on preventing specific nutritional and molecular causes of the pathology they are treating (14). While repeatedly recommending "good nutrition", the broader health network (in the name of "efficiency") seems to be waiting until disease occurs before designing specific treatment for individuals who are clearly in trouble (9). This leaves each person poorly informed about specific foods to

eat to stay healthy. Most people (and their physicians) need much clearer translation of published science into primary prevention programs of specific nutrition information (15). Specific nutrient imbalances that cause cardiovascular death are readily modified by focused prevention education.

Naming a cause of death

Death from coronary heart disease occurs by acute thrombosis and arrhythmia that stop blood flow, often following long-term chronic vascular inflammation (13) that predisposes people to the acute fatal events. Common molecular mechanisms underlying all three processes have origins in the dietary supply of essential nutrients, and they involve synergistic excessive actions of n-6 autacoids produced from those nutrients. Normal self-healing actions of autacoids give reversible fine-tuning of healthy tissue responses, but excessive actions give irreversible pathology. Tissue imbalances among the omega-3 and omega-6 precursors of hormone-like autacoids link food choices to all three synergistic processes. Imbalanced intakes of the essential vitamin-like precursors of eicosanoids cause imbalanced actions of these autacoids. Omega-6 eicosanoids amplify natural responses rapidly enough to shift reversible events occasionally towards irreversible ones, whereas omega-3 eicosanoids are less vigorous in causing irreversible events. These differences in signaling strength are a likely basis for success in the prevention of CVD with seafoods rich in omega-3 fats (16, 17).

Interpreting evidence of cause

A factor closely associated with a disease may be a risk factor that predicts likelihood of developing the disease, a clinical sign that characterizes the disease, or an actual cause of death from the disease. Causal factors in death and disease are what people want to decrease. Four criteria distinguish between risk factors that are causal and those that are not, but each one has limitations.

1. Causal risk factors appear before the signs of disease (and death), but an unrecognized factor could be causing both the risk factor *and* the disease.
2. Incidence of disease (and death) is higher with higher levels of a causal factor, but an unrecognized factor could be increasing both the risk factor and the disease.
3. Controlled clinical intervention against a causal risk factor reduces the incidence or severity of the disease (and death), but the intervention also may have reduced an unrecognized factor and thereby caused both reductions.
4. Plausible mechanisms credibly describe how a causal risk factor contributes to disease pathogenesis (and death),

but experiments that define and recognize molecular mechanisms of disease and death use different conditions, interventions and measurements than clinical trials and epidemiological studies.

This last criterion is most vulnerable to the widespread wish for simple descriptions of complex interactions. Such wishful thinking led to neglect of detailed evidence for plausible (but complex) molecular mechanisms, and it fostered oversimplified attempts at prevention which overlooked evidence for ways to decrease important causal factors.

Agreements among appointed experts form the International Classification of Disease (ICD) that defines the clusters of clinical signs for which the name of a disease such as obesity, diabetes, and hypertension is assigned. In that sense, clinical signs are “determinants” for recognizing the disease (but not necessarily direct causes of death from the disease). Each disease name identifies a cluster of clinical signs, but the mechanisms causing the signs and the mechanisms by which the signs contribute to death need careful interpretation. The three mentioned diseases (obesity, diabetes, and hypertension) plus their associated signs and risk factors are also predictive risk factors for cardiovascular disease and death. Readily modified nutritional imbalances are likely causal factors in all of these disorders. The causal chain of events following from these imbalances needs to be understood in detail and translated into prevention protocols. Attention to mechanisms for the acute fatal event focuses on specific nutrient imbalances that are readily modified by primary prevention programs.

Caution in translating evidence from associated epidemiologic measurements is needed because some signs and risk factors may be only shadows of the true causal factor. For example, grey hair (like advanced age) is a strong predictive associated risk factor for higher death rates, but decreasing the marker by changing hair color or shaving the head will not reverse the underlying mechanisms that contribute to death. There is no plausible mechanism by which grey hair contributes to death. Significant statistical association does not prove cause. In most cases, CHD risk involves synergistic interactions among two or more risk factors, each of which alone may seem only mild in nature. An amplifying synergy gives accelerating rates of death as the number and severity of the factors accumulate with age (Fig 1). Death certificates omit much of the evidence about multiple contributing factors and mechanisms. Thus, epidemiologists have strong certainty in death as an endpoint, but have less certainty as to the causal mechanism of death.

Incorrect assignment of the cause(s) of disease (and death) can waste human and financial resources on ineffective inter-

ventions, and it can delay progress on reducing the true cause(s). Unfortunately, eagerness to assign a causal role may lead to carelessness, like replacing the term “associated with” by a premature judgment expressed as “due to”, “determined by”, “accounted for”, “contributes to”, “effect of”, “increased by”, or “explained by”. Although trained statisticians can recognize and discount careless jargon, the public (and many health professionals) mistakenly believe that such words describing an association indicate an established causal role.

Obsessive attention to blood cholesterol levels was built on associations rather than on a plausible mechanism of death (18). Such misunderstanding leads to widespread disillusionment as the truth eventually and inevitably emerges. This situation is particularly poignant for inadequate information about nutrition and metabolism in cardiovascular disease and death. Widely marketed treatment medications may decrease clinical signs, yet fail to correct the underlying nutritional imbalance that continues to initiate disease processes. This review focuses on readily corrected nutritional imbalances in expenditure/intake of energy and in omega-3/omega-6 essential fatty acids which have plausible mechanisms by which they contribute to fatal events (8, 19).

Diet imbalance as a cause of death

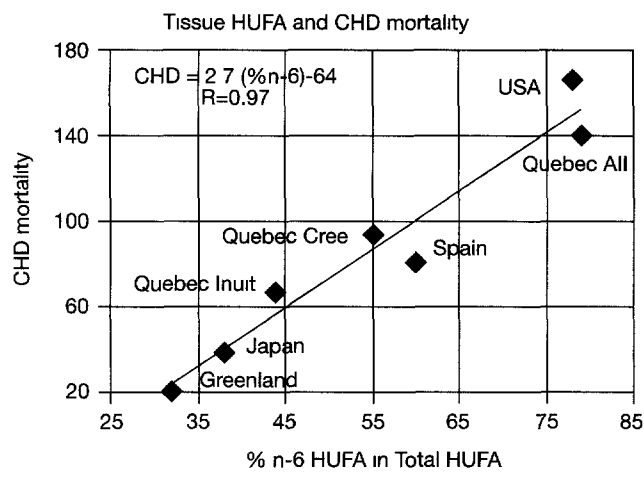
Signaling by hormone-like autacoids gives fine-tuning of many healthy, reversible self-healing responses of body tissues. Tissues form the autacoids from available essential vitamin-like nutrients that originate only from the diet. Important autacoids (and their essential tissue precursors) include histamine (histidine), serotonin (tryptophan), nitric oxide (arginine), and eicosanoids (omega-6 and omega-3 essential fatty acids). Billions of dollars are spent every year to develop and market pharmaceuticals that moderate imbalanced actions of these potent autacoids, but little publicity is given to the fact that the sole source of the precursors for many autacoids is the food that people eat. One important consequence of people’s voluntary food choice is the balance of omega-3 and omega-6 eicosanoid precursors stored in the highly unsaturated fatty acids (HUFA) of tissues (19, 20). These HUFA lead to omega-6 eicosanoids that can amplify vascular inflammatory atherogenesis, platelet thrombogenesis, and heart arrhythmias to such an extent that the normally reversible, physiological responses turn into irreversible pathological events. Plausible mechanisms by which food choices might contribute to early CHD death include the following six processes.

1. Dietary intake determines tissue fatty acid composition.

A diet with high omega-6 relative to omega-3 fats causes tissue HUFA to have high proportions of omega-6 HUFA, pro-

FIGURE 2

Tissue HUFA proportions predict coronary heart disease mortality. The CHD mortality rates are deaths per 100,000 population. Results from USA, Japan, and Greenland were discussed previously (20, 22) as were those from Spain (23), Quebec Inuits (24), Quebec Cree (25), and Quebec overall (26).



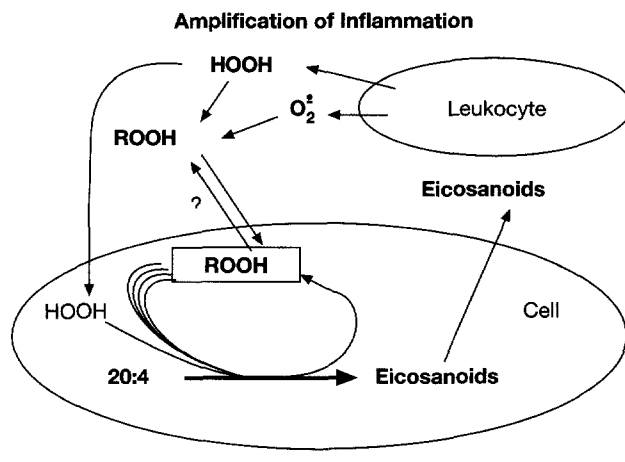
moting rapid formation of omega-6 eicosanoids when stimulated tissue phospholipases release tissue HUFA (21). Tissue HUFA composition is reversibly modified by day-to-day food choices, and it can range between 25% and 85% omega-6 HUFA (20). The impact of dietary essential fatty acids (EFA) on tissue HUFA follows a saturable dose-response relationship (20). A simple calculator uses the predictive equation to show how four types of dietary EFA affect the omega-6 proportion of tissue HUFA (<http://efaeducation.nih.gov/sig/dietbalance.html>). The equation was combined with the USDA Nutrient Database into an interactive computer menu planning program (19) that can be downloaded from <http://ods.od.nih.gov/eicosanoids/> to help people choose foods that create tissue HUFA proportions near any desired target value. The wide diversity in observed tissue HUFA values caused by voluntary food choices is strongly associated ($r = 0.97$) with CHD mortality rates in different populations (Fig 2). Thus, the % omega-6 HUFA in plasma phospholipid HUFA is a biomarker of EFA intakes (20), a predictor of the probable intensity of omega-6 eicosanoid responses (9), and a risk factor for CHD (19). Public health officials should assess the current advice regarding dietary EFA in primary (16) and secondary (17) prevention of CHD to develop and ensure ethically responsible primary prevention advice for people of all ages.

2. **Peroxide amplification of eicosanoid signaling.** ormination of tissue eicosanoids from released non-esterified HUFA involves a transient explosive positive feedback as fatty acid oxygenases (lipoxygenases and cyclooxygenases) form hydroperoxide required for faster synthesis (27). Enzymes forming prostaglandin autacoids (COX-1 and COX-2) act faster with 20:4n-6 than with 20:5n-3 (28, 29). Faster amplification of local oxidant peroxides with omega-6 HUFA explosively accelerates eicosanoid formation and transiently exceeds the rate of inactivation and removal of active autacoid (21). The resulting pulsatile, transient receptor actions range from mild reversible signaling responses to strong actions with irreversible tissue damage, depending on the degree to which non-esterified HUFA and amplifying hydroperoxides accumulate. Thus, elevated levels of tissue oxidants and of non-esterified acids linked to food intake are predictive risk factors for excessive eicosanoid-mediated processes, and they are risk factors for CHD.

3. **Amplification of inflammatory signaling.** Plaques accumulate in vascular regions where eddy currents give blood a longer residence time (30). Prolonged exposure of vessel walls to the positive feedback signals of accumulated inflammatory autacoid mediators tends to amplify the reversible local inflammatory signals and lead to irreversible impairment of vascular endothelium following chronic elevation of inflammatory mediators (e.g., hydrogen peroxide, HOOH, and platelet activating factor, PAF).

FIGURE 3

Peroxide tone triggers and amplifies tissue eicosanoid formation. Hydroperoxide activation of oxygenases enhance eicosanoid signaling (21).



cytokines (e.g., TNF α , IL-1, IL-6), calcium, macrophages and their phagocytic and oxidative products (13, 31). Figure 4 illustrates how local HOOH and other reactive oxygen species (ROS) may amplify cytokine-enhanced protein tyrosine kinase (PTK) action and release the suppression of mitogen activated protein kinase (MAPK) and nuclear factor κ B (NF κ B) while also inactivating PAF acetylhydrolase (AcH). Platelet-activating factor (PAF) amplifies acute inflammatory and thrombotic cascades, and the PAF receptor also responds to oxidized phospholipids to further amplify inflammatory and thrombotic events (32).

Plasma PAF acetylhydrolase (AcH in Fig 4) hydrolyzes and inactivates PAF and the related oxidized phospholipids, suppressing the inflammation. Activation of p38 kinase by high hydroperoxide levels increases acetyltransferase activity for PAF synthesis (33) and amplifies inflammatory signaling. It also increases phospholipase activity that mobilizes arachidonate and its eicosanoid products (34, 35) and amplifies the transcription and release of inflammatory mediators and stress-reactive proteins. Acute phase reactants, orosomucoid and C-reactive protein (CRP) predict greater carotid plaque volume, and orosomucoid is associated with carotid plaques (36). Both were positively associated with levels of triglyceride-rich lipoproteins (VLDL, IDL, LDL) and negatively associated with HDL. After 6, 12 and 36

weeks, two inflammation markers, C-reactive protein (CRP) and serum amyloid A (SAA), were significantly reduced by atorvastatin, but not by simvastatin (37). Both statins lowered secretory phospholipase A2, but they made little change in other inflammatory mediators, IL-6 and ICAM-1.

The intense local inflammatory signaling is diluted greatly as blood moves downstream, although activated leukocytes carry signals further, and acute phase reactants remain in the bloodstream as markers of inflammatory/oxidant stress. Amplified inflammatory signals among the interacting cells are greater when non-esterified omega-6 eicosanoid precursors and oxidant activators are abundant (27), and they drive the normal reversible physiological signals to make undesirable irreversible inflammatory vascular damage that is less with more omega-3 (38). Inflammatory events have long been linked with edema, erythema, hyperalgesia, hyperthermia, and loss of normal tissue function that follows the excessive release and action of eicosanoids and oxidants.

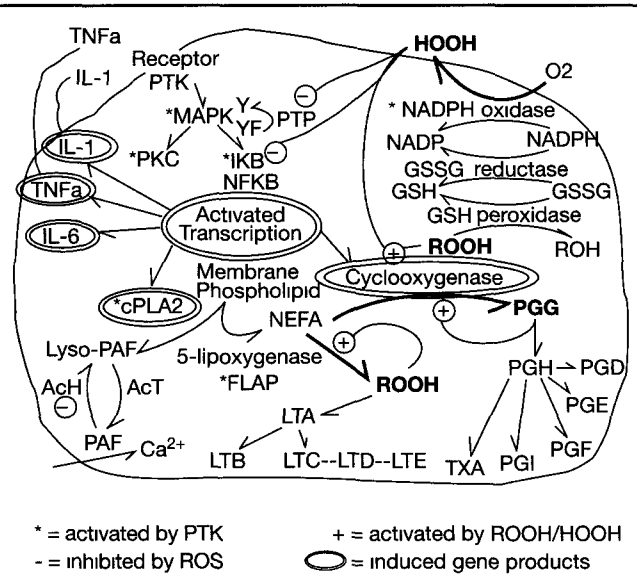
4. Transient postprandial oxidant stress. Elevated levels of glucose and non-esterified fatty acids after large meals promote transient oxidative/inflammatory conditions (39) and activate protein kinase pathways (40) in stress-related response and impair endothelial cell function and vascular physiology (41). Decreased vasodilatation and increased adhesion of leukocytes on vascular walls (42, 43) accompany impaired ability to produce and respond to the self-healing autacoid, nitric oxide (NO). The impairments of vascular endothelium are made worse when local inflammatory oxidants destroy nitric oxide and form toxic peroxynitrite that damages vascular walls (44). High glucose (25 mM) causes ROS generation with p38 MAPK phosphorylation, angiotensinogen (ANG) secretion, and ANG mRNA gene expression; hydrogen peroxide (10 μ M) mimics the glucose effect (40).

Isoprostanes in blood or urine are sensitive markers of oxidative stress and injury (45). Questions remain on the degree to which these products of injury can themselves cause further injury. Homocysteine levels in blood also are associated with chronic oxidant stress and atherosclerosis. Questions remain as to whether the elevated homocysteine observed for people with known vascular disease (46-48) caused the injury or whether they are only markers for oxidant stress. Lowering homocysteine levels by supplemental folic acid and vitamin B12 (49) did not prevent atherosclerosis or vascular dysfunction in monkeys. Apparently, decreasing this marker may not remove the underlying imbalance that causes the oxidative inflammatory disorder.

If the recognized postprandial oxidative/inflammatory

FIGURE 4

Peroxide tone in amplifying inflammatory processes. Abbreviations are noted in the text. Modified from (27) with permission.



events were 99.9% reversible, three meals *per* day would give over 1,000 events annually with only one event (0.1%) remaining as a mild inflammatory focus. However, like compounded interest in a savings account, the 0.1% accumulates year by year in arteries as some reversible fatty streaks progress to inflammatory fibrotic lesions that activate platelets and enhance development of further lesions. Accumulation of meal-associated risk factors over time inexorably makes age a risk factor for CHD death. Thirty or forty years of accumulated inflammatory plaques (12) eventually produced arteries with greater calcium deposits and intimal-medial thickness characteristic of elderly Americans, most likely due to progressive inflammatory disease rather than to "normal aging" (50). Eating more omega-3 EFA may diminish the inflammatory events by displacing tissue precursors of omega-6 eicosanoids.

5. **Platelet-mediated thrombotic events.** Reversible transient platelet aggregates adhering to vessel walls reflect natural signaling events that usually have no pathological consequences. However, stimulated platelets can form and release aggregating factors in an explosive, amplified feedback that forms large aggregates and irreversibly blocks blood flow. Stimulated platelets release HUFA from their membranes (51), and their cyclooxygenase enzyme rapidly leads to a potent (but short-lived) omega-6 autacoid, thromboxane A₂ (52), that further amplifies aggregation. Hydroperoxide activators accelerate the cyclooxygenase reaction, which forms thromboxane that causes still greater platelet action. The explosive amplifications of autacoid formation and platelet adhesion do not occur when the cyclooxygenase is inhibited by aspirin-like anti-inflammatory drugs. Similarly, the explosive aggregatory feedback is attenuated when omega-3 HUFA compete with omega-6 HUFA (53). A platelet-induced transient loss of blood flow (thrombotic ischemia) may cause a reversible deficit of tissue oxygen and energy, whereas too much deficit for too long may give severe and irreversible tissue damage. Omega-6 thromboxane-mediated hyperactivity of blood platelets is a serious diet-related risk factor for CHD death.

6. **Transient arrhythmia.** Impaired local blood flow and heart tissue energy imbalance can be reversed by the increased non-esterified fatty acids released from the hypoxic tissue as its energy balance begins to fail (54). This corrective influence restores oxygen and nutrients and prevents irreversible damage. Healthy autonomic tone that maintains high heart rate variability (55) and suppresses arrhythmia also depends on omega-3 supplies (56, 57). Released omega-6 arachidonic acid (but *not* released

omega-3 acids) forms omega-6 eicosanoids that exacerbate the arrhythmia and lead to irreversible damage of heart tissue and function (58). Although a transient thrombotic ischemic event might initiate a transient arrhythmic event, excessive omega-6 eicosanoids might cause the arrhythmia to be irreversible. Thus, diet choices affect the likelihood of arrhythmia developing from transient ischemia.

The six processes above note how a high proportion of omega-6 HUFA in tissue HUFA over time tends to shift reversible transitory meal-related oxidant stress into irreversible inflammatory, thrombotic and arrhythmic events. The proportion of omega-6 acids in tissue HUFA is a marker of dietary EFA supply, and it is also a CHD risk factor with plausible mechanisms contributing to disease and death. Primary prevention education should show how this risk factor can be lowered by eating foods that increase intake of omega-3 fats and decrease intake of omega-6 fats. Similarly, elevated levels of triglycerides and non-esterified acids in plasma are markers related to food energy balance, and they are also CHD risk factors with plausible mechanisms that contribute to inflammatory oxidative and thrombotic processes amplified by omega-6 eicosanoids. Primary prevention education should show how these synergistic risk factors can be decreased by eating smaller amounts of food energy in individual meals and keeping energy intakes in line with energy expenditures.

Recognizing lipoprotein release from liver

The six processes above recognize atherosclerosis as a chronic and complex vascular inflammatory process in which many immune/inflammatory signals interact synergistically (13). The cholesterol-dependent scientists and marketers properly included plasma lipoproteins in the chain of events that lead from diet to death. However, they were unable to give clear evidence that cholesterol itself was causal, and they created concepts of bad cholesterol and good cholesterol to describe opposite actions of low density lipoprotein complexes (LDL) and high density lipoprotein complexes (HDL). Plasma very low density lipoprotein complexes (VLDL) are released from liver into the blood as the liver responds to the postprandial fatty acids and glucose coming to it. The released triglyceride-rich VLDL is then converted *via* intermediate complexes to LDL by lipoprotein lipase with release of non-esterified fatty acids to tissues that enhance local oxidant stress and endothelial dysfunction. Meal-related stresses may also prompt the liver to release acute phase reactants,

or stress-related proteins, which are also associated with atherogenic conditions (36). Oxidation of LDL by reactive oxygen species released at inflammatory sites can amplify injury because the oxidized phospholipid activates PAF receptors to increase local inflammatory signals. Positive feedback turns the consequences of local inflammation into amplifying factors for more inflammation. Excessive dietary fat and energy intake push liver metabolism to form and release VLDL that increases fatty acid release to plasma while forming LDL. The cholesterol molecules decorating the circulating plasma LDL complexes are loosely described as bad cholesterol, but transient excesses of non-esterified acids are also likely to be harmful.

The HDL complexes include two anti-inflammatory enzymes, paraoxonase and PAF acetyl-hydrolase. These enzymes diminish transient inflammatory conditions that otherwise might be amplified into irreversible pathology. This anti-inflammatory action is a plausible mechanism for the long-recognized beneficial relationship that makes plasma HDL levels an inverse risk factor for CHD mortality (59). Low HDL levels in the elderly (with accumulated inflammatory plaques) are definitely associated with higher mortality (60). Cholesterol molecules decorating HDL lipoprotein complexes are thus associated with beneficial actions of HDL and are loosely described as good cholesterol. An important point here is that the good and bad labels are for actions of the lipoprotein complexes and not the cholesterol molecule itself.

Obsessive attention to blood cholesterol molecules prevented an orderly discussion of evidence for inflammatory stress and autacoid signaling in thrombosis and arrhythmia. The extensive cholesterol education campaigns in the USA did not prevent steadily rising energy imbalances that support vascular inflammatory processes and which may become fatal in combination with imbalanced tissue omega-6 HUFA amplifying those processes. Cholesterol decorating all lipoprotein complexes is a conveniently measured molecule with no defined contribution to inflammation, thrombosis, or arrhythmia that cause cardiovascular death. Plasma cholesterol, mostly made by liver, is a widely discussed biomarker associated with excessive food energy intake, but a plausible mechanism by which cholesterol molecules in plasma contribute to death remains lacking.

Ironically, recent research showed how plasma cholesterol enters cells and beneficially suppresses formation of fat and cholesterol from excess food calories (rather than causing death!). Massive publicity about treating cholesterol as a cause of death has seriously distracted attention from long-standing evidence of the fatal inflammatory,

thrombotic, and arrhythmic mechanisms caused by excessive omega-6 eicosanoid actions. As a result, current advice on food choices for primary prevention has remained poorly linked to known mechanisms for death, and it has failed to recommend specific food choices that could moderate excessive omega-6 eicosanoid amplification of postprandial inflammatory signals.

Beyond a shadow of a doubt

Modern molecular medicine grew explosively throughout the twentieth century. Each newly identified compound accelerated discovery of more previously unknown compounds and functions. Now, there is no doubt that a large complex network of signaling interactions inside cells and between cells participate in a balanced life (and in its cessation, death). A hundred years ago, scientists debated whether potent signaling molecules made in the body should be named hormones (hormain=stir or excite) or autacoids (auto=self, akos=healing). Today's concept of signaling networks regulating body functions includes autacoids and hormones as well as intercellular signaling by cytokines, selectins, and integrins, plus intracellular signaling by protein kinases, protein phosphatases and scaffolding proteins. Some essential nutrients that the body cannot make are called vitamins (vital amines) and others are just essential nutrients. The vitamin-like essential fatty acids (both omega-3 and omega-6) deserve careful attention because many tissues of the body convert them into potent hormone-like autacoids called eicosanoids.

We now know beyond a shadow of a doubt that:

- Fatal heart attacks and thrombotic strokes are caused by excessive platelet omega-6 thromboxane formation and diminished by aspirin-like inhibitors.
- Fatal heart arrhythmias are made worse by the omega-6 arachidonate that forms pro-arrhythmic omega-6 eicosanoids, and they are diminished by many non-esterified fatty acids, especially omega-3 acids.
- Formation and action of omega-6 prostaglandins amplify inflammatory events that are treated worldwide by non-steroidal anti-inflammatory drugs (NSAIDs).
- Inflammation is amplified by positive feedback from released inflammatory mediators at various stages of pathology in vascular atherosclerosis and endothelial dysfunction.
- Inflammatory vascular pathology begins accumulating in adolescents and progresses throughout life, with the current number of inflammatory sites predicting greater future pathology.

- Eicosanoid formation requires initiating and amplifying local hydroperoxides, and elevated tissue hydroperoxides enhance rates of eicosanoid formation.
- Omega-6 eicosanoids amplify natural responses rapidly enough to make some reversible events shift towards irreversible ones, whereas omega-3 eicosanoids are less vigorous in causing irreversible events.
- Stimulated tissues make eicosanoids from non-esterified omega-3 and omega-6 HUFA released from tissue membrane phospholipids.
- The proportions of omega-3 and omega-6 in tissue HUFA are determined by the relative amounts of dietary EFA that compete for incorporation into tissue HUFA.
- Large meals that elevate blood triglycerides, non-esterified fatty acids, and glucose create transient postprandial oxidant stress and increase endothelial dysfunction.
- Four major risk factors (obesity, hypertension, diabetes, smoking) predictive for cardiovascular mortality are themselves associated with endothelial dysfunction, oxidant stress, inflammatory processes, high postprandial blood fat and non-esterified acids, and insulin resistance.
- Higher blood levels of acute phase reactant or stress-reactive proteins (C-reactive protein; heat-shock proteins; orosomucoid; fibrinogen; PAI-1; gamma globulin; angiotensinogen) are systemic markers associated with inflammatory/immune events and oxidant stress.

Summary

The immediate cause of cardiovascular death is thrombosis and arrhythmia that is made worse by excessive omega-6 eicosanoid actions. The chronic vascular inflammation that predisposes to these acute events may be triggered by oxidant stress from postprandial elevations in triglycerides, free fatty acids and glucose, and made worse by a tissue imbalance of omega-3 and omega-6 highly unsaturated fatty acids. The pro-inflammatory imbalance can be prevented by careful choice of food that has more omega-3 and less omega-6. Excessive postprandial elevations of free fatty acids and glucose can be prevented by eating fewer calories *per* meal and by careful balance of overall energy intake and expenditure. Already, many people worldwide voluntarily choose foods that diminish excessive omega-6 eicosanoid actions and prevent cardiovascular death. Primary prevention nutrition recommendations by the American Heart Association in 2000 need more detailed revision and translation to decrease the postprandial inflammatory stress and excessive omega-6 eicosanoid actions that lead to cardiovascular death.

References

- 1 Morgan S, Barer M, Evans R (2000) Health economists meet the fourth tempter: Drug dependency and scientific discourse. *Health Economics* 9: 659-667
- 2 Labarthe DR (1999) Prevention of cardiovascular risk factors in the first place. *Prev Med* 29: S72-S79
- 3 Osaka Declaration (2001) Declaration of the 4th International Heart Health Conference <http://www.med.mun.ca/chhdbc/pdf/Eng%20Osaka%20Declaration.pdf>
- 4 Rosamond WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, Clegg L, Wang CH, Heiss G (1998) Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med* 339: 861-867
- 5 Leaf A (2001) Diet and sudden cardiac death. *J Nutr Health Aging* 5: 173-178
- 6 Murray CJL, Lopez AD (1997) Alternate projections of mortality and disability by cause, 1990-2020: Global Burden of Disease Study. *Lancet* 349: 1498-1504
- 7 Lands WEM, Hamazaki T, Yamazaki K, Okuyama H, Sakai K, Goto Y, Hubbard VS (1990) Changing dietary patterns. *Am J Clin Nutr* 51: 991-993
- 8 Lands WEM (1993) Eicosanoids and health. *Ann NY Acad Sci* 676: 46-59
- 9 Lands WEM (2003) Functional Foods in Primary Prevention or Nutraceuticals in Secondary Prevention? *Curr Top Nutraceutical Res*, 1: 113-120
- 10 PDAY Research Group (1990) Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. A preliminary report from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *JAMA* 264: 3018-3024
- 11 Enos WF, Holmes RH, Beyer J (1953) Coronary disease among United States soldiers killed in action in Korea. *JAMA* 152: 1090-1093
- 12 McGill HC Jr, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, Malcom GT, Tracy RE, Oalmann MC, Strong JP (2000) Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arterioscler Thromb Vasc Biol* 20: 1998-2004
- 13 Ross R (1999) Atherosclerosis – an inflammatory disease. *New Engl J Med* 340: 115-126
- 14 Hobbs FDR, Erhardt L (2002) Acceptance of guideline recommendations and perceived implementation of coronary heart disease prevention among primary care physicians in five European countries: the Reassessing European Attitudes about Cardiovascular Treatment (REACT) Study. *Fam Pract* 19: 596-604
- 15 Lands WEM (2002) Please don't ask me to die faster. *Inform* 13: 896-897

16. Krauss RM, Eckel RH, Howard B, *et al* (2000) AHA Dietary Guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation* 102: 2284-2299
17. Kris-Etherton PM, Harris WS, Appel LJ, for the Nutrition Committee (2002) Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 106: 2747-2757
18. Ravnskov U (2000) *The Cholesterol Myths*. New Trends Publishing, Washington D.C.
19. Lands WEM (2003) Diets could prevent many diseases. *Lipids*, 38: 317-321
20. Lands WEM, Libelt B, Morris A, Kramer NC, Prewitt TE, Bowen P, Schmeisser D, Davidson MH, Burns JH (1992) Maintenance of lower proportions of n-6 eicosanoid precursors in phospholipids of human plasma in response to added dietary n-3 fatty acids. *Biochim Biophys Acta* 1180: 147-162
21. Lands WEM (1979) The biosynthesis and metabolism of prostaglandins. *Ann Rev Physiol* 41: 633-652
22. Lands WEM (1991) Biosynthesis of Prostaglandins. *Annu Rev Nutr* 11: 41-60
23. Chajes V, Elmstahl S, Martinez-Garcia C, Van Kappel AL, Bianchini F, Kaaks R, Riboli E (2001) Comparison of fatty acid profile in plasma phospholipids in women from Granada (southern Spain) and Malmo (southern Sweden). *Int J Vitam Nutr Res* 71: 237-242
24. Dewailly E, Blanchet C, Lemieux S, Sauve L, Gingras S, Ayotte P, Holub BJ (2001) n-3 fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. *Am J Clin Nutr* 74: 464-473
25. Dewailly E, Blanchet C, Gingras S, Lemieux S, Holub BJ (2002) Cardiovascular disease risk factors and n-3 fatty acid status in the adult population of James Bay Cree. *Am J Clin Nutr* 76: 85-92
26. Dewailly EE, Blanchet C, Gingras S, Lemieux S, Sauve L, Bergeron J, Holub BJ. (2001) Relations between n-3 fatty acid status and cardiovascular disease risk factors among Quebecers. *Am J Clin Nutr* 74: 603-611
27. Kulmacz RJ, Lands WEM (1997) Peroxide tone in eicosanoid signaling. In: Forman HJ, Cadenas E (eds) *Oxidative stress and signal transduction*. Chapman & Hall, New York, pp 134-156
29. Malkowski MG, Thuresson ED, Lakkides KM, Rieke CJ, Micielli R, Smith WL, Garavito RM (2001) Structure of eicosapentaenoic and linoleic acids in the cyclooxygenase site of prostaglandin endoperoxide H synthase-1. *J Biol Chem* 276: 37547-37555
30. Giddens DP, Zarins CK, Glagov S (1993) The role of fluid mechanics in the localization and detection of atherosclerosis. *J Biomech Eng* 115: 588-594
31. Libby P (2002) Inflammation in atherosclerosis. *Nature* 420: 868-874
32. Zimmerman GA, McIntyre TM, Prescott SM, Stafforini DM (2002) The platelet-activating factor signaling system and its regulators in syndromes of inflammation and thrombosis. *Crit Care Med* 30 (Suppl 5): S294-S301
33. Sakamoto H, Tosaki T, Nakagawa Y (2002) Overexpression of phospholipid hydroperoxide glutathione peroxidase modulates acetyl-CoA, 1-O-Alkyl-2-lyso-sn-glycero-3-phosphocholine acetyltransferase activity. *J Biol Chem* 277: 50431-50438
34. Pawliczak R, Huang XL, Nanavaty UB, Lawrence M, Madara P, Shelhamer JH (2002) Oxidative stress induces arachidonate release from human lung cells through the epithelial growth factor receptor pathway. *Am J Respir Cell Mol Biol* 27: 722-731
35. Hayama M, Inoue R, Akiba S, Sato T (2002) ERK and p38 MAP kinase are involved in arachidonic acid release induced by H(2)O(2) and PDGF in mesangial cells. *Am J Physiol Renal Physiol* 282: F485-F491
36. Gronholdt ML, Sillesen H, Wiebe BM, Laursen H, Nordestgaard BG (2001) Increased acute phase reactants are associated with levels of lipoproteins and increased carotid plaque volume. *Eur J Vasc Endovasc Surg* 21: 227-234
37. Wiklund O, Mattsson-Hulten L, Hurt-Camejo E, Oscarsson J (2002) Effects of simvastatin and atorvastatin on inflammation markers in plasma. *J Intern Med* 251: 338-347
38. Thies F, Garry JMC, Yaqoob P, Rerkasem K, Williams J, Shearman CP, Gallagher PJ, Calder PC, Grimble RF (2003) Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 361: 477-485
39. Bae JH, Bassenge E, Kim KB, Kim YN, Kim KS, Lee HJ, Moon KC, Lee MS, Park KY, Schwemmer M (2001) Postprandial hypertriglyceridemia impairs endothelial function by enhanced oxidant stress. *Atherosclerosis* 155: 517-523
40. Hsieh TJ, Zhang SL, Filep JG, Tang SS, Ingelfinger JR, Chan JS (2002) High glucose stimulates angiotensinogen gene expression via reactive oxygen species generation in rat kidney proximal tubular cells. *Endocrinology* 143: 2975-2985
41. Griendling KK, Sorescu D, Lassegue B, Ushio-Fukai M (2000) Modulation of protein kinase activity and gene expression by reactive oxygen species and their role in vascular physiology and pathophysiology. *Arterioscler Thromb Vasc Biol* 20: 2175-2183
42. Jagla A, Schrezenmeir J (2001) Postprandial triglycerides and endothelial function. *Exp Clin Endocrinol Diabetes* 109: S533-S547
43. Hyson DA, Pagheroni TG, Wun T, Rutledge JC (2002) Postprandial lipemia is associated with platelet and monocyte activation and increased monocyte cytokine expression in normolipemic men. *Clin Appl Thromb Hemostas* 8: 147-155
44. Ceriello A (2002) Nitrotyrosine: new findings as a marker of postprandial oxidative stress. *Int J Clin Pract* 129: 51-58
45. Morrow JD, Roberts LJ (2002) The isoprostanes: their role as an index of oxidant stress status in human pulmonary disease. *Am J Respir Crit Care Med* 166: S25-S30
46. Harker LA, Slichter SJ, Scott CR, Ross R (1974) Homocystinemia, vascular injury and arterial thrombosis. *N Engl J Med* 291: 537-543
47. McCully KS (1996) Homocysteine and vascular disease. *Nat Med* 2: 386-389

48. Wang G, Siow YL, O K (2000) Homocysteine stimulates nuclear factor kB activity and monocyte chemoattractant protein-1 expression in vascular smooth muscle cells. a possible role for protein kinase C. *Biochem J* 352: 817-826
49. Lentz SR, Piegors DJ, Malinow MR, Heistad DD (2001) Supplementation of atherogenic diet with B-vitamins does not prevent atherosclerosis or vascular dysfunction in monkeys. *Circulation* 103: 1006-1011
50. Rumberger JA, Sheedy PF 2nd, Breen JF, Fitzpatrick LA, Schwartz RS (1996) Electron beam computed tomography and coronary artery disease. scanning for coronary artery calcification. *Mayo Clin Proc* 71: 369-377
51. Weaver BJ, Holub BJ (1986) The relative degradation of [14C] eicosapentaenoyl and [3H]arachidonoyl species of phosphatidylinositol and phosphatidylcholine in thrombin-stimulated human platelets. *Biochem Cell Biol* 64: 1256-1261
52. Hamberg M, Svensson J, Samuelsson B (1975) Thromboxanes, a new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc Natl Acad Sci USA* 72: 2994-2998
53. Lands WEM, Culp BR, Hirai A, Gorman R (1985) Relationship of thromboxane generation to the aggregation of platelets from humans: Effects of eicosapentaenoic acid. *Prostaglandins* 30: 819-825
54. Kang JX, Leaf A (1994) Effects of long-chain polyunsaturated fatty acids on the contraction of neonatal rat cardiac myocytes. *Proc Natl Acad Sci U S A* 91: 9886-9890
55. Chessa M, Butera G, Lanza GA, Bossone E, Delogu A, De Rosa G, Marietti G, Rosti L, Carminati M (2002) Role of heart rate variability in the early diagnosis of diabetic autonomic neuropathy in children *Herz* 27: 785-790
56. Christensen JH, Skou HA, Madsen T, Torring I, Schmidt EB (2001) Heart rate variability and n-3 polyunsaturated fatty acids in patients with diabetes mellitus. *J Intern Med* 249: 545-552
57. Christensen JH, Skou HA, Fog L, Hansen V, Vesterlund T, Dyerberg J, Toft E, Schmidt EB (2001) Marine n-3 fatty acids, wine intake, and heart rate variability in patients referred for coronary angiography. *Circulation* 103: 651-657
58. Li Y, Kang JX, Leaf A (1997) Differential effects of various eicosanoids on the production or prevention of arrhythmias in cultured neonatal rat cardiac myocytes. *Prostaglandins* 54: 511-530
59. Despres JP, Lemieux I, Dagenais GR, Cantin B, Lamarche B (2000) HDL-cholesterol as a marker of coronary heart disease risk: the Quebec cardiovascular study. *Atherosclerosis* 153: 263-272
60. Corti MC, Guralnik JM, Salive ME, Harris T, Field TS, Wallace RB, Berkman LF, Seeman TE, Glynn RJ, Hennekens CH, *et al* (1995) HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA* 274: 539-544